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Processing and storage effects on water vapor sorption by some model pharmaceutical solid dosage formulations

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Abstract

Several excipients and their formulations were equilibrated at relative humidities and temperatures selected to simulate typical pharmaceutical storage and processing conditions. Three different water detection techniques—loss on drying, Karl Fischer coulometry and an automatic moisture balance, were used to determine the moisture content of these systems. The excipients all possessed very different water sorption tendencies, as did their formulations. Isothermal water sorption by the dry blends, granules and tablets of each formulation was identical, suggesting that the processes involved in tablet manufacturing did not affect the water sorption behavior. Accurate water content predictions for the formulations were possible by adding the contribution of water from each excipient. Such predictions may be helpful for defining upper and lower water content specifications and storage conditions for excipients and their formulations. © 1997 Elsevier Science B.V.

Keywords: Excipient; Formulation; Water vapor sorption; Loss on drying; Karl Fischer coulometry; Moisture balance

1. Introduction

The ubiquitous presence of water in the atmosphere enables it to be readily sorbed by solid pharmaceutical materials during processing and storage. The amount of water that is sorbed is dependent on the chemical identity and polarity of the compound, as well as on the relative humidity and temperature (Zografi and Hancock, 1994). The amount and location of water in a system are important due to the potential of water to cause or worsen chemical and physical stability (Ahlneck and Zografi, 1990). Quantitation of water in pharmaceutical materials is sometimes difficult due to the ease in which water can travel

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via the vapor state. Fortunately several analytical water detection techniques exist which range in sensitivity and practicality (Komatsu et al., 1994). Concomitant use of these methods should allow us to achieve a better understanding of their limitations, accuracy and reproducibility, as well as to determine exactly how water interacts with pharmaceutical solids.

Pharmaceutical solid dosage formulations are often subjected to thermal and mechanical processes, such as blending, sieving and drying, which may change their water sorption tendencies. By determining the water content of dry blends, granules and tablets of the same formulation, the effects of such processes on water sorption behavior may be identified. Each drug or excipient and consequently each formulation has a different tendency for water sorption. If the water content of a mixture is simply the sum of the water sorbed by its components then predictions for simple formulations based on the properties of individual excipients might be made.

The objective of this work was to determine the water content of some typical pharmaceutical excipients and their formulations after equilibration at a range of temperatures and relative humidities conditions using several different analytical techniques. Comparison of the behavior of the different materials and the analytical methods could then be made. In addition, the effects of several processing operations and the accuracy of simple water content predictions were to be evaluated.

2. Experimental

2.1. Materials

The excipients and chemicals used are listed in Table 1.

Table 1
Materials used for experiments

Excipients	Supplier
Microcrystalline cellulose NF (MCC)	FMC Corp.
Pregelatinized starch NF (Starch 1500)	Colorcon Inc.
Lactose monohydrate NF	Mallinckrodt Canada Inc.
Hydroxypropyl cellulose NF (HPC) (Klucel EXF)	Hercules Canada Inc.
Magnesium stearate NF	Mallinckrodt Canada Inc.
Reagents	
KF reagent Hydranal Coulomat AG	Hoechst Canada Inc.
Hydranal Coulomat CG	Hoechst Canada Inc.
Methanol 99.9% (anhydrous)	Omnisolv Inc.
Salts	
Potassium acetate	American Chemicals Ltd.
Magnesium nitrate	Aldrich Inc.
Sodium chloride	American Chemicals Ltd.
Sodium tartrate dihydrate	American Chemicals Ltd.
Sodium indomethacin trihydrate	Merck Inc.

2.2. Preparation of dry blends, granules and tablets

The compositions of the three model formulations are displayed in Table 2. Dry blends of each of the three formulations were prepared by mixing in a high shear mixer/granulator for 5 min. The granules were made by an additional 5 min of mixing with 25% added water. The wet granules formed were dried in a fluid bed dryer and passed through a cone mill with a 0.050 inch screen. After lubrication with 0.5% magnesium stearate in a V-blender, the dry granules were compressed into 15/32 inch diameter, 400 mg weight, round, standard biconvex tablets on a rotary tablet press.

Table 2
Composition of formulations A, B and C (% w/w)

Raw material	Formulation (%)		
	A	B	C
MCC	49.75	48.25	—
Starch	49.75	—	49.75
Lactose	—	48.25	49.75
HPC	—	3.00	—
Magnesium stearate	0.50	0.50	0.50

Samples of the raw materials, dry blends, dry granules and tablets were stored in desiccators at controlled relative humidities and temperatures (21, 50, 75% RH and 5, 30, 50°C). Saturated salt solutions were used to maintain the desired humidities (Nyqvist, 1983). The tablets were stored at all three temperatures whereas the raw materials, dry blends and granules were stored at 30°C only. After equilibrating at the various conditions (>4 weeks), multiple samples ($n=3$) were analyzed using Karl Fischer coulometry, loss on drying and a moisture balance, and their mean water contents were reported.

2.3. Karl Fischer analysis (KF)

A DL37 coulometric titrator was employed (Mettler, NJ). The accuracy and reproducibility of the Karl Fischer reagent were verified with hydranal 1.00 water standards. An average of six 60 ml methanol injections were used as the blank. The methanol was then used to prepare between 6–10 samples for analysis. Samples were weighed in tared glass lyophilisation vials after which 12 ml of methanol was accurately introduced. The vials were carefully crimped to seal them from atmospheric moisture and each vial was sonicated for 15–30 min. While remaining in the crimped vials the samples were centrifuged at 3000 r.p.m. for 15 min. An average of four to six titrations was then used to determine the amount of water present in the supernatant liquid.

2.4. Loss on drying analysis (LOD)

Samples were dried at 60°C under a vacuum of 127 Torr for 24 h and their water content calculated from their loss in weight. The samples were then dried further at 105°C for 24 h and reweighed.

2.5. Moisture balance (MB)

A calibrated MB-300G moisture balance was employed (VTI, FL). Approximately 7–10 mg of sample was used for each analysis. The samples were initially dried in the instrument at 60°C under vacuum (3×10^{-2} Torr) for 1 h, and then sequentially exposed to 0–90% relative humidity in 10% RH steps at 30°C. Sorption equilibrium at each relative humidity was judged to have been reached when a weight change of less than 5 μg occurred in three consecutive 10 min periods. It was assumed that the total weight change from the initial value was indicative of the quantity of water sorbed.

2.6. Prediction of the percent moisture in formulations

The water content of the formulations at any given humidity (RH_1) was predicted by using Eq. (1).

$$W_{mix} = \sum\{(W_a m_a) + (W_b m_b) + \cdots\} \quad (1)$$

where W_{mix} is the water content of mixture at RH_1; W_a is the water content of raw material a at RH_1; and m_a is the weight fraction of raw material a in mixture.

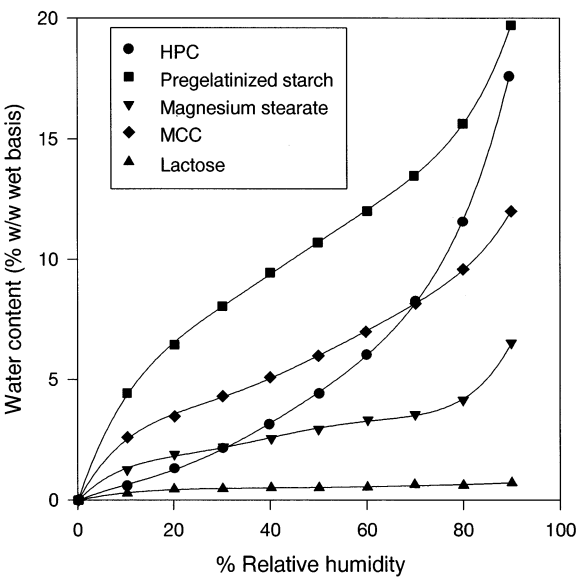

Fig. 1. Water content of excipients as a function of percent relative humidity by MB method.

Table 3
Equilibrium moisture content of raw materials exposed to different relative humidities at 30°C

Material	% RH	Method of analysis			
		LOD (60°C)	LOD (105°C)	KF	MB
MCC	22	3.24 ± 0.02	4.76 ± 0.06	4.25 ± 0.02	3.67
	52	5.52 ± 0.07	6.54 ± 0.30	6.62 ± 0.01	6.06
	75	7.20 ± 0.08	8.30 ± 0.27	7.85 ± 0.00	8.86
HPC	22	2.05 ± 0.04	2.56 ± 0.05	1.69 ± 0.01	1.48
	52	4.61 ± 0.02	5.30 ± 0.06	4.42 ± 0.01	4.58
	75	7.24 ± 0.01	7.95 ± 0.11	8.71 ± 0.01	9.76
Starch	22	6.34 ± 0.06	9.35 ± 0.03	9.02 ± 0.06	6.71
	52	10.27 ± 0.14	12.06 ± 0.07	11.55 ± 0.04	10.62
	75	12.36 ± 0.15	14.00 ± 0.07	13.48 ± 0.09	14.94
Lactose	22	0.44 ± 0.08	5.18 ± 0.26	5.46 ± 0.08	0.49
	52	0.78 ± 0.30	6.06 ± 0.05	5.43 ± 0.00	0.50
	75	0.40 ± 0.01	6.26 ± 0.16	5.42 ± 0.01	0.55
Magnesium stearate	22	1.68 ± 0.15	—	2.41 ± 0.01	1.89
	52	1.59 ± 0.04	—	2.41 ± 0.02	2.95
	75	1.85 ± 0.10	—	2.34 ± 0.00	3.87

Values represent mean % water ± S.D.

3. Results and discussion

3.1. Method accuracy and suitability

Two crystal hydrates (sodium tartrate dihydrate and sodium indomethacin trihydrate) were used as standards for the water determination techniques (not shown). For both, the loss on drying analysis at 105°C proved to be the most accurate resulting in less than 1% deviation from the theoretical values (15.7 and 12.5%, respectively). LOD at 60°C and the moisture balance at low relative humidity gave results that were significantly less than the theoretical values. No KF result was obtained for the sodium tartrate standard due to its insolubility in the KF reagent. The accuracy of the methods clearly depends as much on the type of sample as on the actual technique used.

3.2. Water sorption by the excipients and their formulations

The excipients all exhibited very different tendencies for water sorption (Fig. 1, Table 3). The results obtained were practically identical to those reported previously (Wade and Weller, 1994). The water content of the three polymer excipients rose in a sigmoidal fashion with increasing relative humidity and was very high at elevated humidities as expected (Hancock and Zografi, 1993). The water content of the crystalline lactose monohydrate remained relatively constant at all humidities. No results for water content of magnesium stearate by LOD at 105°C are reported because of thermal degradation at this temperature. A formulation's water uptake should reflect the water uptake tendencies of its component excipients (Table 5). Formulation A, containing primarily pregelatinized starch and microcrystalline cellu-

Table 4
Effect of temperature on the water content of the tablet formulations at 75% R.H. by KF analysis

Temperature (°C)	Formulation A	Formulation B	Formulation C
5	14.74	8.13	12.02
30	11.50	6.64	9.93
50	10.86	6.45	9.66

Values represent mean % water.

Table 5
Experimental equilibrium moisture contents of formulations A, B and C at 30°C

Material	% RH	Method of analysis			
		LOD (60°C)	LOD (105°C)	KF	MB
Dry blend A	22	4.16 ± 0.11	7.16 ± 0.08	5.86 ± 0.01	4.70
	52	6.63 ± 0.10	9.74 ± 0.08	8.23 ± 0.02	7.77
	75	8.24 ± 0.18	11.54 ± 0.09	10.71 ± 0.01	11.22
Dry blend B	22	1.52 ± 0.04	5.71 ± 0.19	4.55 ± 0.02	1.79
	52	2.42 ± 0.05	6.29 ± 0.26	5.35 ± 0.01	3.08
	75	3.56 ± 0.03	7.15 ± 0.10	6.51 ± 0.03	4.85
Dry blend C	22	2.35 ± 0.07	7.38 ± 0.02	6.79 ± 0.02	3.30
	52	3.70 ± 0.10	8.92 ± 0.07	8.14 ± 0.02	5.41
	75	5.24 ± 0.11	10.35 ± 0.03	9.57 ± 0.04	7.62
Granules A	22	2.91 ± 0.15	6.65 ± 0.03	6.32 ± 0.01	4.67
	52	5.80 ± 0.24	9.22 ± 0.06	8.70 ± 0.02	8.49
	75	8.42 ± 0.09	12.12 ± 0.38	10.91 ± 0.03	11.95
Granules B	22	1.53 ± 0.03	4.94 ± 0.02	4.24 ± 0.01	1.62
	52	2.57 ± 0.02	6.37 ± 0.34	5.29 ± 0.02	2.96
	75	3.96 ± 0.02	7.39 ± 0.10	6.48 ± 0.02	4.70
Granules C	22	2.92 ± 0.05	7.54 ± 0.17	6.64 ± 0.02	3.11
	52	4.31 ± 0.11	9.21 ± 0.31	8.02 ± 0.02	5.58
	75	6.27 ± 0.20	10.75 ± 0.02	9.45 ± 0.04	8.00

Values represent mean % water ± S.D.

lose had the highest water uptake. The formulation containing both pregelatinized starch and lactose, formulation C, possessed a higher moisture content than formulation B, a mixture of lactose and microcrystalline cellulose. The mixtures therefore behaved qualitatively similar to their components. A quantitative analysis of this relationship is presented later in this paper.

3.3. Method comparison

The LOD method at 105°C generally detected the most amount of water followed by the KF method (Tables 3–5). The MB and the LOD method at 60°C detected lesser amounts of water for all formulations and excipients. The KF technique proved to be very reproducible with standard deviation values on the order of 0.01–0.1% water for the analysis of three different samples. The LOD results at 60°C were the most scattered due to only partial sample drying. The LOD results at 105°C were better with standard deviations ranging from 0.06 to 0.30% water. A properly calibrated Karl Fischer instrument should produce the most satisfactory results for soluble materials both in terms of reproducibility and total water content. Karl Fischer analyses also have the advantage of causing no thermal stress in the analyte.

A plot of LOD at 60 and 105°C versus KF for the tablet formulations shows the relative amounts of water detected by these three methods (Fig. 2). A near linear relationship for both sets of data indicates that each method gives reproducible results across the entire range of water content and formulations studied. The positive y-intercept for the 105°C-LOD plot suggests that at low water contents loss on drying at 105°C detects greater amounts of water than the KF analysis. The slopes of less than one for both plots indicate that as the water content increases, KF analysis detects an increasing proportion of the total water present. From a water content of about 9% onwards, KF water detection is greater

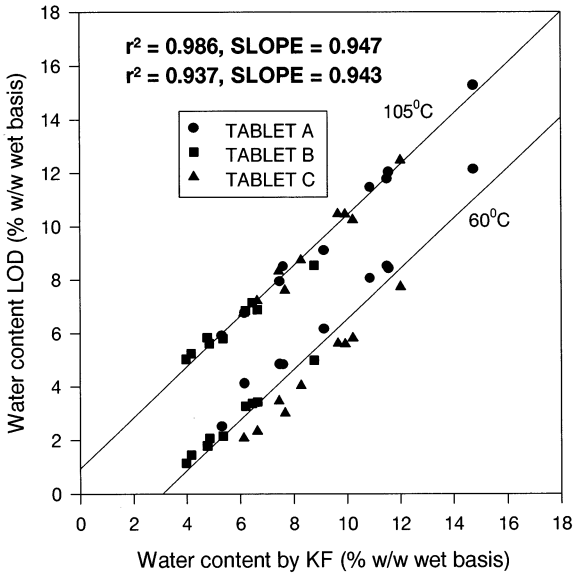

Fig. 2. Comparison of KF and LOD results for water content in tablets.

than LOD at 105°C. Drying at 60°C detects significantly less water than either of the other two methods. By carefully inspecting the LOD at 60°C versus KF plot, it is evident that drying at this temperature removes less water for tablets B and C than for A relative to the KF analysis. This is probably because formulations B and C contain lactose monohydrate which does not release all of its water of hydration at this temperature. The slopes of the lines of best fit (not shown) are nearly identical however, indicating that a constant proportion of the water of hydration is being detected by LOD at 60°C.

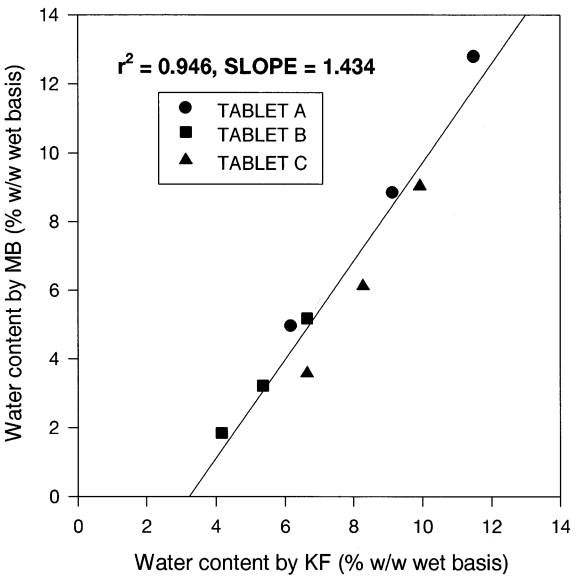

Fig. 3. Comparison of KF and MB results for water content in tablets.

A plot of MB versus the KF results for the tablets demonstrates fair linearity (Fig. 3), but it should be noted that the MB detects a lower proportion of water at lower moisture contents resulting in a correlation with a slope significantly greater than unity. The MB experiments involve drying the sample at the start of the experiment, whereas none of the others do. This 'pre-treatment' could affect the results. It does allow all data points to be considered as absorption data whereas the other methods may include a combination of absorption and desorption data depending upon the initial moisture content of the raw materials. A comparison of the MB results and LOD at 60°C (Tables 5 and 6) show increasingly higher water contents detected by the MB method as the RH increases. This could be due to the different vacuum conditions used for drying, the different sample sizes or the effects of pre-drying the samples. Trends found in the 60°C LOD and the MB data can still be considered valid because of the good correlation with the KF results, but the phenomenon of partial sample drying should be noted and values not be considered to be absolute.

3.4. Temperature effects

The data in Table 4 and Table 6 demonstrate that increased moisture uptake occurred at lower temperatures for all three formulations. At 75% RH, tablets of formulation A sorbed 4% more water at 5°C than at 30°C. Similar behavior has been reported for other pharmaceutical excipients (Weiser, 1985). Formulations exposed to low temperatures might be adversely affected by an increase in water sorption if they are moisture sensitive. This has important implications for the storage and handling of pharmaceutical products.

Table 6
Equilibrium moisture content of formulation A tablets exposed to various temperaturesand relative humidities

Experimental conditions		Method of analysis			
Temperature (°C)	% RH	LOD (60°C)	LOD (105°C)	KF	MB
5	23	4.85 ± 0.07	7.94 ± 0.05	7.48 ± 0.06	—
	59	8.44 ± 0.09	12.04 ± 0.32	11.56 ± 0.06	—
	76	12.14 ± 0.05	15.28 ± 0.09	14.74 ± 0.11	—
30	22	4.13 ± 0.15	6.77 ± 0.09	6.17 ± 0.01	4.96
	52	6.17 ± 0.07	9.11 ± 0.01	9.14 ± 0.04	8.85
	75	8.52 ± 0.16	11.78 ± 0.33	11.50 ± 0.03	12.8
50	22	2.52 ± 0.05	5.91 ± 0.06	5.32 ± 0.00	—
	46	4.83 ± 0.10	8.50 ± 0.27	7.62 ± 0.02	—
	75	8.06 ± 0.09	11.47 ± 0.24	10.86 ± 0.04	—

Values represent mean % water ± S.D.

3.5. Processing effects

The moisture balance results (Fig. 4) demonstrate that there was very little difference in water sorption for the dry blend, granule and tablet forms of formulation A, and this was true of formulations B and C as well. The KF and LOD results (Tables 5 and 6) also demonstrate negligible differences between the different forms of the same formulations. These result suggest that no interactions exist between the excipients after processing which affect their water sorption behavior (Chinacoti, 1988). Accurate predictions of water content based on the raw materials found in the formulations may therefore be feasible.

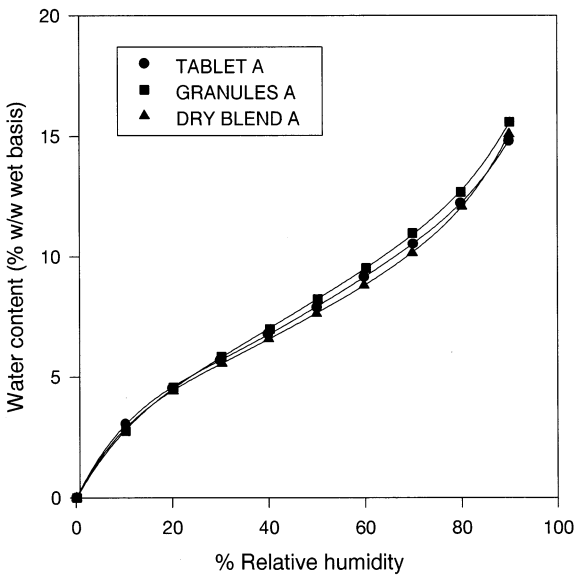

Fig. 4. Water content of formulation A as a function of percent relative humidity by MB method.

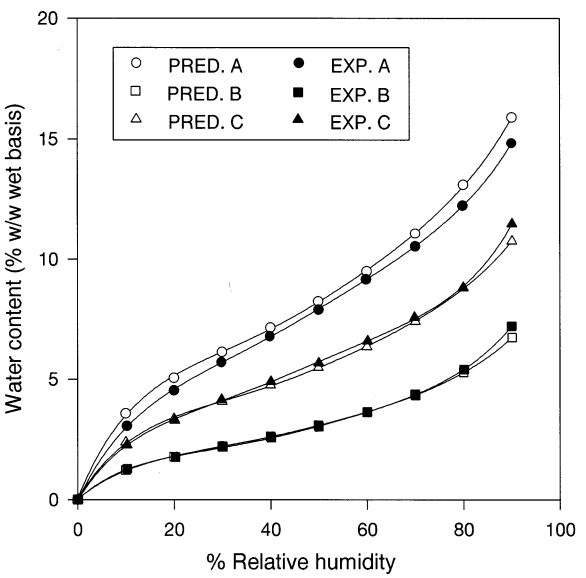

Fig. 5. Predicted and experimental water sorption isotherms by MB for formulations A, B and C.

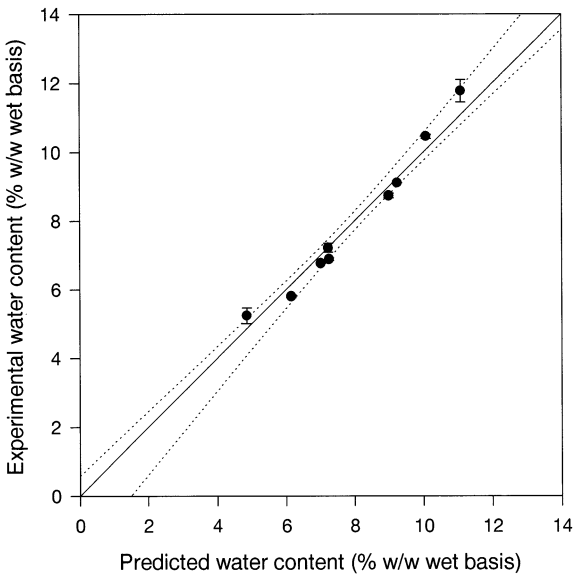

Fig. 6. Experimental versus predicted water content for tablets stored at various relative humidity at 30°C (LOD 105°C).

3.6. Water content predictions

Predictions were made using Eq. (1) for the water in the formulations. Predictions of sorbed water contents based on the MB data produced very similar results to experimental values (Fig. 5). Predictions for the total water contents were also successfully made using the KF and LOD data. Fig. 6 is a plot of predicted values versus experimental values for the LOD at 105°C. A straight line with an intercept of 0 and slope of 1 corresponding to a perfect correlation is drawn onto the graph. The actual data points obtained from analysis are relatively close to the ideal indicating that water content predictions are fairly accurate over the entire range of water contents.

By acquiring sorption isotherms of each formulation component, it appears to be feasible to predict the amount of water present in such formulations at any relative humidity. This should enable formulation scientists to more easily determine the optimum water content specifications for similar products. The upper and lower limits of water content, which have been set arbitrarily in the past, could be selected to correspond to specific relative humidities and the acceptable range of water contents could then be predicted. Table 5 and Table 6 display the range of water contents for formulations A, B and C at 25 and 75% relative humidity at 30°C. The water content specification of a 'typical' batch could be the average value of these upper and lower limits, or could correspond to the value at 50% relative humidity. This procedure is only valid for formulations where the effects of material interactions are minimal. This is unlikely to be a general result and potential effects of excipient-excipient and drug-excipient interactions should always be investigated.

4. Conclusions

All the techniques used in this study for water content determinations were found to be very reproducible when carefully performed. The results varied according to the material being tested and the suitabilities of the technique used. Large differences in the water sorption behavior of the excipients were evident and consequently the behavior of the formulations also varied considerably. The formulations containing significant amounts of pregelatinized starch sorbed the highest amount of water at all humidities while the formulations which contained a large proportion of lactose generally had lower water contents. The temperature effects on water sorption were small but significant. Dry blending, wet granulation, fluid bed drying and compression processes did not cause any significant effect on the water sorption behavior of the formulations. Predictions of water content based on the sum of the water in the individual excipients proved to give accurate results. Such predictions may be useful for determining suitable storage conditions for moisture sensitive formulations and for assigning the upper and lower limits for water content specifications.

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